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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,830	VON DER MULBE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-16 and 24-28) in the reply filed on 7/1/2005 is acknowledged. The traversal is on the ground(s) that claim 17 of Group II and claim 18 of Group III are drawn to methods of using the pharmaceutical composition of Group I and are related to the composition of Group I, claims 17 and 18, and that the search of Groups I-III can be done without any additional search burden since the inventions are classified in the same class and subclass. This is not found persuasive because the search of the product is not coextensive with the search of the methods. The search of the product will not necessarily identify the claimed methods because the claimed product can be used in different processes as indicated on pages 3-4 of the restriction requirement mailed 6/1/2005. Although the products and methods have been classified in the same class and subclass, the search of the methods will require a separate text search of the patent and non-patent literature for the claimed method steps not encompassed by the product. The additional searching that would be required to search more than one group would impose a serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. An examination on the merits of claims 1-16 and 24-28 follows.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt of the certified copy of the foreign priority document, DE 101 27 283.9, is acknowledged. These papers have been placed of record in the file.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 6/30/2005, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action. The information disclosure statement filed 6/30/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. A copy of the WO 01/04313 A1 reference was not provided. Therefore, the WO 01/04313 A1 reference has not been considered.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration.
Non-initialed alterations have been made to the addresses for Ingmar Hoerr and Steve Pascolo. See 37 CFR 1.52(c).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

At page 12, paragraph [0045], the specification contains a nucleic acid sequence that is not referred to by the use of a sequence identifier. Where the description or claims of a patent application discuss a sequence that is set forth in the Sequence Listing, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. The nature of the non-compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below.

Claim Objections

Claims 19-28 are objected to because of the following informalities: the claims depend from a claim that has been withdrawn as reading on a non-elected invention. Appropriate correction is required.

Claims 1-7 and 11 are objected to because of the following informalities: the use of the phrase "peptide or polypeptide" is redundant. The specification does not provide clear definitions that differentiate between the two terms. Dorland's Illustrated Medical Dictionary

defines a "peptide" as any member of a class of compounds of low molecular weight that yield two or more amino acids on hydrolysis and defines "polypeptide" as a peptide that on hydrolysis yields more than two amino acids. Thus, the terms are equivalent. It would be remedial to amend the claims to recite only "polypeptide" as depend claim 11 further modifies the polypeptide of claim 11. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2-5, 24 and 26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 11/025,858 (hereinafter '858) in view Pavlakis et al (US Patent No. 5,965,726; see the entire reference).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226

(Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

In the instant case, conflicting claim 18 is drawn to a vaccine comprising a modified mRNA that is stabilized and/or translation-optimized. The composition of claim 18 differs from instant claims 1, 2-5, 24 and 26 in that it does not recite stabilization by increasing GC content or optimizing translation by replacing codons recognized by a rare cellular tRNA with a codon recognized by an abundant tRNA. Pavlakis et al teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier nucleic acid molecule comprising mutations to remove inhibitory instability (INS) regions of an mRNA by making an AT rich region more GC rich without altering the amino acid sequence encoded by the mRNA (e.g. column 11, lines 45-67; column 12, lines 1-30; claim 25). Further, Pavlakis et al teach the mutation of an INS to contain more preferred codons as opposed to less-preferred codons (i.e. codons recognized by rare cellular tRNA) (e.g. column 12, lines 7-50). Moreover, Pavlakis et al teach that the removal of the instability elements will allow increased expression of the mRNA (e.g. column 1, lines 49-61). Therefore, it would have been obvious to modify the vaccine composition of claim 18 of the '858 Application such that the stability of the modified mRNA is increased by removing an instability element through increasing the GC content of the element, and by optimizing translation using preferred codons. One having ordinary skill in the art would have been motivated to make such a modification to achieve increased mRNA and stability, as per the teachings of Pavlakis et al.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-16, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "modified wild type mRNA" in line 6. There is insufficient antecedent basis for this limitation in the claim. It is unclear whether the phrase "modified wild type mRNA" is referring to the wild type RNA or the modified RNA. Thus, the phrase "wherein the modified wild type mRNA and the modified mRNA encode a peptide or polypeptide comprising an identical amino acid sequence" is unclear. For the purposes of examination, the phrase has been interpreted as comparing the wild type mRNA to the modified mRNA, wherein both mRNA sequences encode an identical peptide or polypeptide.

Claim 24 is vague and indefinite in that the metes and bounds of the phrase "nucleic acid sequence generated by the method of claim 19" are unclear. The phrase is unclear in that the method of claim 19 appears to result in a nucleic acid sequence in the form of written characters rather than an actual nucleic acid molecule comprising the necessary chemical subunits and covalent bonds linking the subunits. Because, claims 26-28 claim a pharmaceutical composition comprising the nucleic acid sequence of claim 24, claims 24 and 25 have been interpreted as being drawn to an isolated nucleic acid molecule comprising the nucleic acid sequence generated by the method of claim 19.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to or encompass a set of modified mRNA molecules comprising fewer destabilizing elements relative to that of a wild type sequence or having no destabilizing elements. The claims do not require that the mRNA destabilizing element have any particular conserved structure. Thus, the claims are drawn to a genus of mRNA molecules defined by the absence of a nucleic acid sequence defined by function.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. Regarding mechanisms of mRNA destabilization, the specification states that many of the mechanisms were unknown at the time the invention was made (e.g. paragraph [0010]). The specification notes that sequence of eukaryotic mRNAs frequently include destabilizing sequence elements (DSE) to which signal proteins can bind and regulate the enzymatic degradation of the mRNA *in vivo* (e.g. paragraph [0034]). DSEs may be located in

the coding region or non-translated regions of the mRNA (e.g. paragraph [0034]). The specification describes "AURES" sequences as AU-rich sequences that occur in the 3' UTR of a number of unstable mRNAs (e.g. paragraph [0035]). The specification describes the sequence GAACAG, which is found in the 3' UTR of the gene encoding the transferrin receptor (e.g. paragraph [0035]). Further, the specification envisions the elimination of sequences recognized by endounucleases (e.g. paragraph [0035]). However, consensus endonuclease recognition sequences are not described for any endonuclease capable of degrading single-stranded RNA or double-stranded RNA resulting from hairpin formation. No description is provided of any other DSE.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of two destabilizing elements known in the art. The results are not necessarily predictive of other destabilizing elements. The AU-rich sequences do not have a shared structure with the GAACAG element of the transferrin receptor. Thus, it is impossible for one to extrapolate from the examples described herein those destabilizing elements that would necessarily meet the structural/functional characteristics of the rejected claims. For one to remove the destabilizing element from the mRNA, one would have to be able to recognize the structure of a destabilizing element. Adequate description is not provided by the instant specification of a representative number of destabilizing elements.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a representative number of destabilizing elements that would allow the identification of destabilizing elements in any mRNA. AU-rich elements are known to consist of

two domains: Domain 1 contains 40-50 nucleotides, is AU-rich and includes several AUUUA pentamers, and Domain 2 is a 20 nucleotide U-rich region found in a subset of AU-rich elements (Ross, TIG, Vol. 12, No. 5, pages 171-175, 1996; e.g. page 171, left column, last paragraph). AU-rich elements may be present in as many as 5-8% of human genes (Wilusz et al., TIG, Vol. 20, No. 10, pages 491-497, 2004; e.g. page 491, left column). The GAACAAG sequence of the transferrin receptor, which is described in the instant specification, is an endonuclease recognition sequence (Ross, 1996; e.g. page 173, Endoribonucleases). Prior to the time the invention was made, it was known in the art that the mutation of the transferrin endoribonuclease recognition sequence to CCCCCCC blocks cleavage (Ross, 1996; e.g. page 173, Endoribonuclease). Ross states that "We believe that mammalian cells contain only few mRNases none of which are 'restriction RNases' analogous to restriction endodeoxyribonucleases" (page 171, mRNA degradation signals and mRNA-binding proteins that influence mRNA stability). Although the endoribonucleases may be key effectors of mRNA degradation, the enzymes responsible for the cleavage events and the sequences that are recognized by the endonucleases were not identified, except for a few transcripts such as the mRNA encoding the transferrin receptor and the AUUUA site of the AU-rich element (Tourriere et al., Biochimie, Vol. 84, pages 821-837, 2002; e.g. page 827-827, section 4.3). No description is provided by the prior art with regard to the sequences that are recognized by endoribonucleases. Furthermore, the specification teaches that the many of the mechanisms that destabilize RNA are still unknown (e.g. paragraph [0010]). Around the time the invention was made, a database containing sequences and functional elements of 5' and 3' untranslated regions of eukaryotic mRNAs was established (Pesole et al. Nucleic Acids Research, Vol. 30, No. 1,

pages 335-340, 2002). However, Pesole et al teach that a statistically significant match to a database sequence does not necessarily mean that the sequence has biological significance (e.g. paragraph bridging pages 338-339). Moreover, the post-filing art indicates that prediction of how an mRNA will decay based on its sequence is not possible, and the mechanism by which regulation of mRNA decay is achieved remains obscure in many cases (Wilusz et al, 2004; e.g. page 495, What next?).

Given the very large genus of destabilizing elements encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the sequence of destabilizing elements other than AU-rich elements, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of destabilizing elements that are to be removed from the mRNA sequence. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those destabilizing elements that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1, 6 and 7.

Claims 1 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to or encompass a set of modified mRNA comprising 5' and/or 3' stabilization sequences. The claims do not require that the mRNA stabilizing element have any particular conserved structure. Thus, the claims are drawn to a genus of mRNA molecules defined by the presence of a nucleic acid sequence defined by function.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes a stabilization element of the general formula (C/U)CCAN$_x$CCC(U/A)Py$_x$UC(C/U)CC, which is found in the 3'UTR of mRNAs that encode α-globin, α-(I)-collagen, 15-lipoxygenase, and tyrosine hydroxylase (e.g. paragraph [0045]). The specification teaches that the untranslated sequences of the *Homo sapiens* and *Xenopus laevis* β-globin genes are capable of functioning as stabilization elements. No description is provided of any other stabilization element.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of a few examples of stabilization elements. The results are not necessarily predictive of other sequences that are capable of functioning as stabilization elements. Although the examples provided in the specification are limited to untranslated sequences of mRNA, which are capable of functioning as stabilization elements, all untranslated regions are not capable of functioning as stabilization elements. In fact, as taught in the instant specification, some untranslated regions contain destabilizing elements (e.g. paragraph [0034]). Furthermore,

the specification teaches that the many of the mechanisms that stabilize RNA are still unknown (e.g. paragraph [0010]). Thus, it is impossible for one to extrapolate from the few examples described herein those 5' and 3' stabilization elements that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of 5' and 3' ribonucleic acid sequences capable of functioning as stabilization sequences. The 5' cap and 3' polyA tail are known to influence mRNA stability (Mitchell et al. Current Opinion in Cell Biology, Vol. 13, No. 3, pages 320-325, 2001; e.g. page 320, Introduction). Around the time the invention was made, a database containing sequences and functional elements of 5' and 3' untranslated regions of eukaryotic mRNAs was established (Pesole et al. Nucleic Acids Research, Vol. 30, No. 1, pages 335-340, 2002). However, Pesole et al note that a statistically significant match to a database sequence does not necessarily mean that the sequence has biological significance (e.g. paragraph bridging pages 338-339). Moreover, the post-filing art indicates that prediction of how an mRNA will decay based on its sequence is not possible, and the mechanism by which regulation of mRNA decay is achieved remains obscure in many cases (Wilusz et al, 2004; e.g. page 495, What next?).

Given the very large genus of sequences encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the sequence structure required to confer stability to mRNA, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of 5' and 3' stabilization elements. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in

the art to envision those 5' stabilization elements that satisfy the functional limitations of the claims. Furthermore, one structural element is fully described for the 3' UTR; however, this single type of stabilization element is insufficient to describe the broad genus of stabilization elements encompassed by the claim. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1 and 8.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 6, 11-15, 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Pavlakis et al (US Patent No. 5,965,726; see the entire reference).

Regarding claims 1, 3 and 6, Pavlakis et al teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier nucleic acid molecule comprising mutations to remove inhibitory instability (INS) regions of an mRNA by making an AT rich region more GC rich without altering the amino acid sequence encoded by the mRNA (e.g. column 11, lines 45-67; column 12, lines 1-30; claim 25). Further, Pavlakis et al teach the mutation of an INS to contain more preferred codons as opposed to less-preferred codons (i.e. codons recognized by rare cellular tRNA) (e.g. column 12, lines 7-50). Thus, Pavlakis et al teach modified mRNA

with increased GC content, the ability to encode the identical polypeptide, fewer codons recognized by rare cellular tRNAs, and reduced number of destabilizing sequence elements.

Regarding claim 11, 13 and 14, Pavlakis et al teach the mutation of mRNAs encoding growth factors, viral antigens, E. coli 6-phosphogluconate dehydrogenase and btoB, and secreted polypeptides (e.g. column 13, lines 7-41; column 23-24; column 50, lines 30-60). The polypeptides encoded by the mRNAs are antigens with multiple epitopes capable of being recognized by antibodies produced by a host organism. It is known in the art that one antigen may have multiple epitopes (Roitt, Brostoff and Male. Immunology, 4th Edition. Barcelona: Times Mirror International Publishers Limited, 1996, page 1.7).

Regarding claim 12, Pavlakis et al teach the mutation of mRNAs encoding HIV-1 env (e.g. column 1, lines 32-37; column 23, lines 15-25; claim 28). Env polypeptide is processed and secreted (e.g. column 10, line 10).

Regarding claim 15, Pavlakis et al teach the mutation of mRNAs encoding cytokines such as interferons and interleukins (e.g. column 23, lines 15-25).

Regarding claim 24, Pavlakis et al teach nucleic acid molecules that have been modified to generate a nucleic acid molecule with increased stability, wherein the nucleic acid sequence and the modified nucleic acid sequence encode an identical polypeptide (e.g. e.g. column 11, lines 45-67; column 12, lines 1-30).

Regarding claim 26, Pavlakis et al teach a composition comprising a modified nucleic acid molecule and a pharmaceutically compatible carrier (e.g. column 11, lines 45-67; column 12, lines 1-30; claim 25).

Claims 1, 8, 9 and 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Felgner et al (US Patent No. 5,580,859; see the entire reference).

Regarding claim 1, Felgner et al teach pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a modified mRNA that encodes a polypeptide, wherein the modified mRNA and wild type mRNA encode a polypeptide having an identical amino acid sequence (e.g. column 4, lines 32-45; column 5, lines 7-20; column 8, lines 28-29). Modifications taught by Felgner et al include capping the mRNA, circularizing the mRNA, or chemically blocking the 5' end of the mRNA (e.g. column 9, lines 14-27).

Regarding claim 8, Felgner et al teach pharmaceutical compositions, wherein the modified mRNA comprises a 5' cap structure or a 5' untranslated sequence that does not require a 5' cap for translation (i.e. an internal ribosomal entry site, IRES) (e.g. column 11, lines 35-63; column 24, lines 30-67; column 25, lines 1-36). Further, Felgner et al teach the use of *Xenopus* β-globin flanking untranslated sequences (e.g. column 28, lines 4-20). The specification teaches that the *Xenopus* β-globin untranslated sequences are stabilization sequences (e.g. paragraph [0045]). Thus, Felgner et al teach 5' and 3' stabilization sequences.

Regarding claim 9, Felgner et al teach pharmaceutical compositions, wherein the modified mRNA comprises at least one analogue of a naturally occurring nucleotide such as a an amino-7-dUTP nucleotide to block the 5' or 3' end from RNase (e.g. column 12, lines 15-30).

Regarding claims 11-14, Felgner et al teach pharmaceutical compositions comprising modified mRNA molecules encoding growth hormone, cytokines (e.g. interleukins and interferons), tumor antigens, viral antigens or pathogen antigens (e.g. column 21, lines 56-67; column 22, lines 1-15). The polypeptides encoded by the mRNAs are antigens with multiple

epitopes capable of being recognized by antibodies produced by a host organism. It is known in the art that one antigen may have multiple epitopes (Roitt, Brostoff and Male. Immunology, 4th Edition. Barcelona: Times Mirror International Publishers Limited, 1996, page 1.7).

Regarding claim 15, Felgner et al teach pharmaceutical compositions further comprising an mRNA species that encodes an interferon or interleuckin-1 (e.g. paragraph bridging columns 22-23).

Regarding claim 16, Felgner et al teach pharmaceutical compositions further comprising a cytokine in the form of an mRNA or polypeptide (e.g. paragraph bridging columns 22-23; column 8, lines 35-40).

Claims 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (WO 99/20774; see the entire reference).

Regarding claims 24 and 26, Chen et al teach a vaccine comprising a modified nucleic acid sequence with increased GC content, and increased frequency of codons recognized by abundant cellular tRNAs (e.g. page 3). Thus, Chen et al necessarily teach a composition comprising a modified nucleic acid and a pharmaceutically acceptable carrier.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11-16, 24 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 99/20774; see the entire reference) in view of Felgner et al (US Patent No. 5,580,859; see the entire reference).

The teachings of Chen et al are described above and applied as before. Further, Chen et al teach a modified MSP-1 nucleic acid, wherein all rare codons are replaced with preferred codons, and all mRNA instability motifs are eliminated (e.g. page 3). Further, Chen et al teach that the replaced codons code for the same amino acids as the wild type codon (e.g. page 3). Chen et al teach a modified MSP-1 nucleic acid that has a G/C content increased at least 15% relative to that of wild type mRNA encoding the MSP-1 polypeptide (e.g. SEQ ID NO: 1, 45.5% GC; SEQ ID NO: 2, 24.2% GC). MSP-1 is an antigen that is expressed during the life cycle of the protozoan *P. falciparum* (e.g. page 1, lines 25-34). The MSP-1 polypeptide encoded by the modified nucleic acid is an antigen with multiple epitopes capable of being recognized by antibodies produced by a host organism. It is known in the art that one antigen may have multiple epitopes (Roitt, Brostoff and Male. Immunology, 4th Edition. Barcelona: Times Mirror International Publishers Limited, 1996, page 1.7).

Chen et al do not teach a modified nucleic acid that is a modified mRNA comprising a cap structure or IRES, and at least one analog of a naturally occurring nucleotide. Chen et al do not teach a pharmaceutical composition comprising a cytokine or an adjuvant.

Felgner et al teach pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a modified mRNA that encodes a polypeptide, wherein the modified mRNA and wild type mRNA encode a polypeptide having an identical amino acid sequence (e.g. column 4, lines 32-45; column 5, lines 7-20; column 8, lines 28-29). Modifications taught by Felgner et al include capping the mRNA, circularizing the mRNA, or chemically blocking the 5' end of the mRNA (e.g. column 9, lines 14-27). Felgner et al teach pharmaceutical compositions, wherein the modified mRNA comprises a 5' cap structure or a 5' untranslated sequence that does not require a 5' cap for translation (i.e. an internal ribosomal entry site, IRES) (e.g. column 11, lines 35-63; column 24, lines 30-67; column 25, lines 1-36). Felgner et al teach pharmaceutical compositions, wherein the modified mRNA comprises at least one analogue of a naturally occurring nucleotide such as an amino-7-dUTP nucleotide to block the 5' or 3' end from RNase (e.g. column 12, lines 15-30). These modifications of the mRNA retard degradation of the mRNA in the cell (e.g. column 9, lines 15-27). Further, the mRNA is preferred because it does not self-replicate, does not integrate into the genome, and allows transient expression of a gene product (e.g. column 6, line 38, to column 8, line 35). Felgner et al teach pharmaceutical compositions comprising modified mRNA molecules encoding growth hormone, cytokines (e.g. interleukins and interferons), tumor antigens, viral antigens or pathogen antigens (e.g. column 21, lines 56-67; column 22, lines 1-15). Felgner et al teach that is advantageous to include a cytokine in the form of a polypeptide or polynucleotide (e.g. column 8, lines 35-41). Felgner et

al teach pharmaceutical compositions further comprising a cytokine in the form of an mRNA or polypeptide (e.g. paragraph bridging columns 22-23; column 8, lines 35-40).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid vaccine of Chen et al to include a 5' modified mRNA, cytokine and adjuvant taught by Felgner et al because Chen et al and Felgner et al teach it is within the ordinary skill in the art to use nucleic acid as a vaccine for pathogens.

One would have been modified to use a modified mRNA because the mRNA does not self-replicate or integrate into the genome as taught by Felgner et al. Further, one would have been motivated to modify the 5' end of the mRNA to increase the stability of the molecule as taught by Felgner et al. Moreover, one would have been motivated to modify the vaccine to include a cytokine or adjuvant in order to receive the expected benefit of an enhanced immune response to the vaccine as taught by Felgner et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 3, 6, 9-15, 24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (US Patent No. 5,965,726; see the entire reference) in view of Ueda et al (Nucleic Acids Research, Vol. 19, No. 3, pages 547-552, 1991; see the entire reference).

The teachings of Pavlakis et al are described above and applied as before.

Pavlakis et al do not teach a modified mRNA comprising at least one analogue of a naturally occurring nucleotide.

Ueda et al teach mRNA molecules comprising phosphorothioate nucleotide analogs (e.g. pages 548-549, Enzymatic synthesis of phosphorothioate-containing RNAs, and Analysis of the phosphorothioates incorporated into RNAs). Ueda et al teach that mRNA comprising phosphorothioate ribonucleotides is more stable in *in vitro* translation systems (e.g. pages 549-550, Stability of phosphorothioate RNAs). Further, Ueda et al teach that more protein can be synthesized from a phosphorothioate-modified mRNA (e.g. page 551, right column, 3rd and 4th paragraphs).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include a phosphorothioate nucleotide analog of Ueda et al in the modified mRNA of Pavlakis et al because Ueda et al teach it is within the ordinary skill in the art to use phosphorothioates in mRNA molecules and Pavlakis et al teach modified mRNA molecules.

One would have been motivated to make such a modification in order to receive the expected benefit of increased stability of the mRNA as taught by Ueda et al. Further, one would have been motivated to make such a modification in order to receive the expected benefit of increased translation products as a result of the increased mRNA stability as taught by Ueda et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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